The Role of Surgery in the Treatment of Limited Disease Small Cell Lung Cancer

Time to Reevaluate

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Abstract: Chemo-radiation is considered the standard procedure for the management of limited disease small-cell lung cancer (SCLC). Controversy remains as to when surgery should be considered. We sought to determine the survival after complete resection of SCLC and the prognostic impact of clinical and pathologic stage.

Methods: A retrospective review was undertaken of patients who underwent surgery between 1980 and 2006. Patients were staged according to the 6th edition of the Tumor, Node, Metastasis classification of lung cancer, actuarial survival estimated with Kaplan Meier methods and comparisons were undertaken using Cox regression.

Results: We identified 59 patients who underwent complete resection with nodal dissection for SCLC. The mean age (SD) was 62 (11) years and 41 (69%) were men. Clinical staging information was available in 53, listed by stage with IA (n = 9), IB (n = 21), IIA (n = 0), IIB (n = 13), IIIA (n = 9), IIIB (n = 1). The median time to follow-up (1st to 3rd quartile) was 2.8 (0.79–8.65) years with an overall survival (95% confidence interval) at 1 and 5 years of 76% (65, 88), 52% (40, 68). There were no clear differences in the survival of patients in clinical T categories (p = 0.366) with good overall results in patients across the spectrum of nodal disease from N0 to N2 (p = 0.498).

Conclusions: This study shows excellent survival for stage I to III patients who underwent lung resection with nodal dissection for SCLC and supports the need to reevaluate surgery as primary treatment and use of clinical Tumor, Node, Metastasis criteria in the selection of patients with very limited disease for surgery.

Key Words: Small cell, Surgery, Lung cancer.

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Combined modality therapy using chemotherapy and thoracic irradiation is currently the standard of care for limited-stage small cell lung carcinoma. However, cumulative results from 25 years of North American chemo-radiation trials reported a current median survival of 17 months [1] and data from the Surveillance, Epidemiological and End Results program of the National Cancer Institute (Bethesda, Maryland) reported an overall 5 year survival of 10%.[2]

Surgery has been considered unsuitable for patients with limited stage disease as it had been associated with overall 5 year survival of less than 5%.[3] Early randomized trials comparing surgery alone versus radiotherapy reported 4%[4] survival at 2-years in patients randomized to surgery alone and a 20% 2-year survival in patients randomized to surgery after initial response to chemotherapy.[5]

The Veterans Administration staging is adequate in clinical practice and trials of chemo-radiation. However, limited stage disease (confined to the ipsilateral hemithorax) constitutes a heterogeneous population. A refinement to the staging has been proposed with a "very limited disease" category assigned to patients with limited stage disease without mediastinal nodal involvement.[6]

Some regard surgery as the appropriate treatment of a peripheral small cell lung carcinoma without nodal involvement[7] or with very limited stage disease, but there remains uncertainty if and when surgery best fits into the treatment modality for limited-stage small cell lung carcinoma.

The aims of this study is to ascertain results of surgical treatment and to evaluate the impact of stage on survival in patients with completely resected very limited-stage subgroup of patients with small cell lung cancer.

METHODS

A review was undertaken of patients who underwent surgery for SCLC between 1980 and 2006 at the Royal Brompton Hospital. Cases were identified from the pathology archive up until 1999 and from a prospective lung cancer resection database thereafter. All slides were reviewed by one pathologist (AGN) and classified according to current histologic criteria for neuroendocrine tumors. All patients undergoing surgery for small cell lung carcinoma underwent nodal dissection.[8] The standard workup for lung resection in the 1990 decade was computed tomography (CT) thorax and routine mediastinoscopy and this changed in the 2000 decade to CT thorax and routine integrated positron emission tomography (PET)/CT scanning to assess for mediastinal (and distant) disease with mediastinoscopy for patients with me-

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diastinal uptake. Clinical and pathologic staging was undertaken according to the 6th edition of the TNM classification of lung cancer.[9] Patients within this group had been previously reported as a subgroup of neuroendocrine tumors.[10]

After consultation with our institutional review board chairman, it was deemed that this study fulfilled the criteria for a "service evaluation" as defined with the National Research Ethics Service and it presented no ethical issue and did not require formal research ethics committee review.

Data Acquisition

Individual patient data were collated from a prospective histopathology database, patients case notes and autopsy reports. Mortality was determined using the National Health Service strategic tracing system (National Health Service, United Kingdom) and survivors contacted by telephone for interview.

TABLE 1. Baseline Characteristics

Number		59
Mean age, years (SD)		62 (11)
Men, *n* (%)		41 (69)
Pathology		
Pure small cell, *n* (%)		43 (73)
Small cell and LCNEC, *n* (%)		8 (14)
Small cell and other combination, *n* (%)		8 (14)
	Clinical	Pathologic
T category		
N/A[a]	6 (10)	2 (3)
T1	11 (19)	15 (25)
T2	37 (63)	38 (64)
T3	6 (7)	3 (5)
T4	1 (2)	1 (2)
	Clinical	Pathologic
N category		
N/A[a]	6 (10)	4 (7)
N0	31 (53)	18 (31)
N1	15 (25)	21 (36)
N2	7 (12)	16 (27)
	Clinical	Pathologic
Stage		
N/A[a]	6 (10)	4 (7)
IA	9 (15)	5 (8)
IB	21 (36)	11 (19)
IIA	0 (0)	4 (7)
IIB	13 (22)	18 (31)
IIIA	9 (15)	16 (27)
IIIB	1 (2)	1 (2)
Operation, *n* (%)		
Pneumonectomy	26 (44)	
Lobectomy	26 (44)	
Bilobectomy	4 (7)	
Non anatomical	2 (3)	
Not documented	1 (2)	

[a] N/A, Insufficient detail available for classification.

Statistical Analysis

Categorical data are presented as frequency (%) and continuous data as mean with standard deviation (SD) or median with 1st and 3rd quartile. Probabilities of survival were estimated using the Kaplan-Meier method. Cox proportional hazards regression models were used to ascertain the association between individual factors and survival.

RESULTS

From January 1, 1980 to January 1, 2007, a total of 59 patients underwent complete R(0) resection for small cell lung carcinoma. The diagnosis of SCLC was known preoperatively in 20 patients, 10 of whom had nodal disease (7 cN1, 3 cN2). No patient in this series had any documentation of preoperative chemotherapy. The mean age (SD) was 62 (11) years and 41 (70%) were men. The pathologic subtype was pure small cell lung carcinoma in 43 (73%) of patients and small cell in combination with another tumor type in the remaining 16 cases. Clinical and post surgical pathologic staging information was available in 53 and 55 patients respectively. In total, 21 patients underwent mediastinoscopy and lymph node biopsies, of which 4 were positive for N2 disease. Baseline characteristics, stage and operation extent are summarized in Table 1. Postoperatively, it was documented that 13 patients had received adjuvant chemotherapy, 2 patients received adjuvant radiotherapy, and 1 patient received adjuvant chemo-radiotherapy.

The median time to follow-up (1st to 3rd quartile) was 2.8 (0.79–8.65) years with an overall survival (95% confidence interval) at 1 and 5 years of 76% (65, 88) and 52% (40,

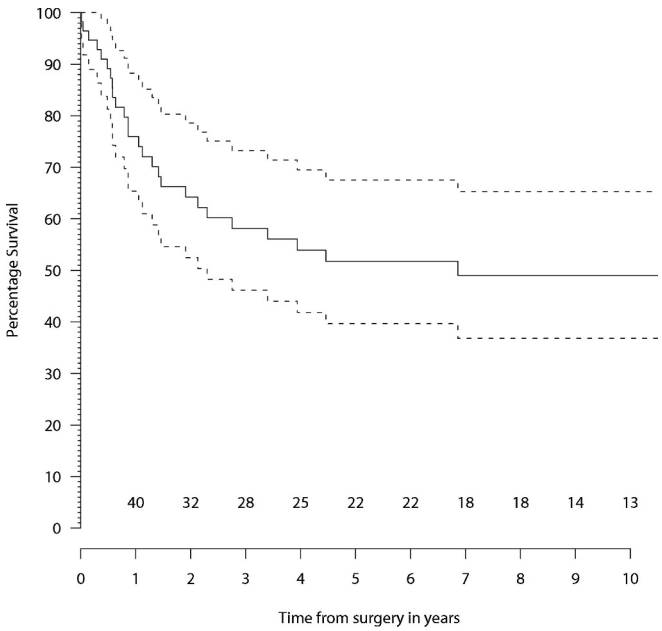

FIGURE 1. Overall survival (95% confidence interval) after lung resection for small cell lung cancer. Numbers at risk are presented per year.

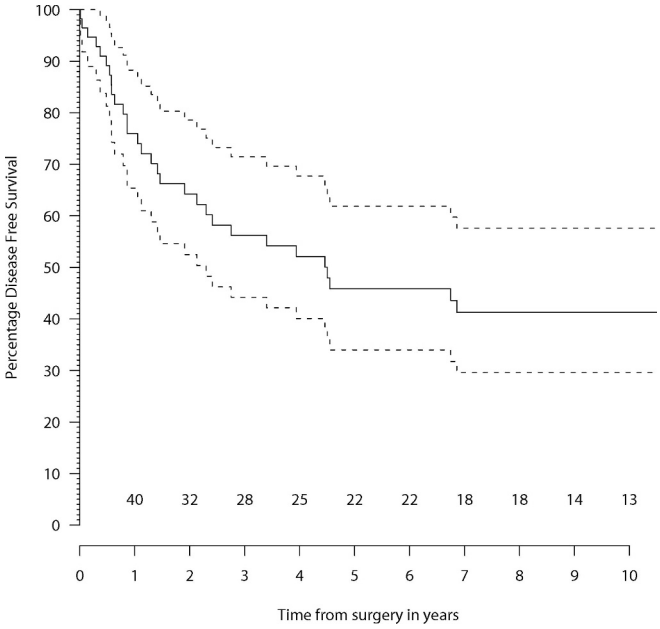

FIGURE 2. Disease free survival (95% confidence interval) after lung resection for small cell lung cancer. Numbers at risk are presented per year.

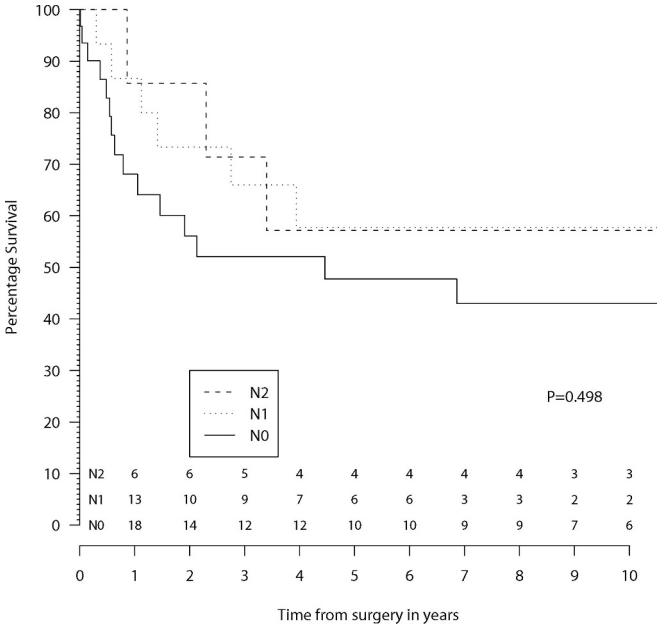

FIGURE 3. Survival by clinical nodal status after complete resection. Numbers at risk are presented per year.

68), respectively (Figure 1). The disease free survival at 1 and 5 years was 76% (65, 88) and 46% (34, 62), respectively (Figure 2).

There were no significant differences in the survival of patients with pure small cell lung carcinoma and those with small cell lung carcinoma in conjunction with another tumor type ($p = 0.509$). There was no difference in survival across

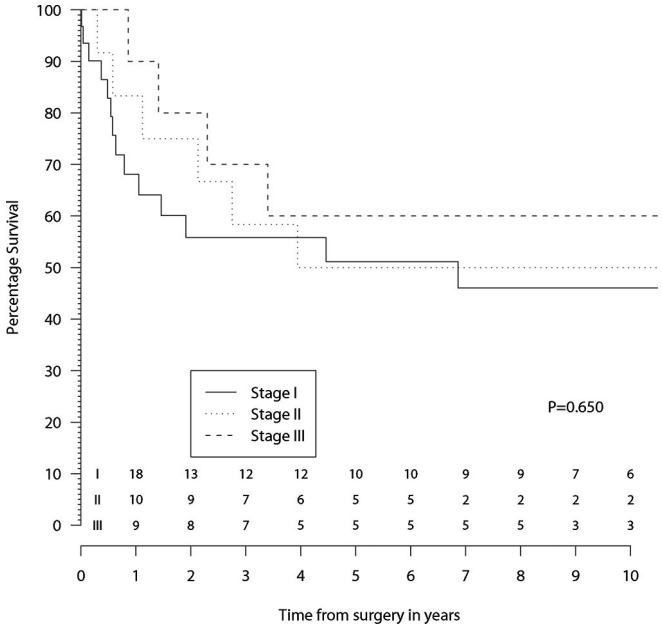

FIGURE 4. Survival by UICC clinical stage grouping after complete resection. Numbers at risk are presented per year.

TABLE 2. Univariable Risk Factors for Death

	Hazard Ratio	95% Confidence Interval	*p*
Age, per decade increase	1.52	1.00–2.31	0.05
Female sex	0.68	0.27–1.69	0.41
Mixed pathology	1.34	0.56–3.20	0.51
T category			
cT1	1.00	NA	NA
cT2	2.28	0.67–7.70	0.19
cT3 or 4	1.79	0.30–10.80	0.52
N category			
cN0	1.00	NA	NA
cN1	0.49	0.24–1.62	0.33
cN2	0.58	0.17–2.02	0.40
Overall clinical stage			
cI	1.00	NA	NA
cII	0.84	0.32–2.18	0.71
cIII	0.60	0.20–1.82	0.36

NA, not applicable.

clinical T ($p = 0.366$) or clinical N categories ($p = 0.489$), with good survival in all nodal categories after complete resection (Figure 3). This resulted in poor discrimination of survival in clinical Union Internationale Contre le Cancer (UICC) stage grouping ($p = 0.650$, Figure 4), with increasing age as the only significant predictor of mortality after complete surgical resection (Table 2).

The results were similar when analyzed using pathologic stage and no significant differences in survival were noted across the pathologic T ($p = 0.331$) or pathologic N ($p = 0.597$) categories.

DISCUSSION

From 2003–2005 we performed 267 lung resections for non-small cell lung cancer and correspondingly, 6 procedures for small cell lung cancer in this time frame. We estimate that the lung resections performed for small cell lung cancer comprises approximately 2% of our work load. In many cases, the decision to operate was an active decision, based on assessment of resectability of the primary tumor.

The results of our study reveal good survival in this selected subgroup of patients in UICC stages I to III who underwent lung resection of pure and combined small cell lung carcinoma. In this series, there were no clear differences in the outcome of patients across clinical and pathologic T and N categories, and after surgical resection, UICC classification had a poor discriminatory value for prognosis.

Previous Trials

The role of surgery for the treatment of limited-stage small cell lung carcinoma has been considered inappropriate due to poor overall survival. The most widely cited supporting evidence of lack of benefit for surgical treatment was an early Medical Research Council randomized trial of surgery versus radiotherapy.[4] Patients were recruited based on bronchial biopsies and complete resection was only achieved in 34 (48%) of patients, possibly reflecting the unavailability of CT scanning and nonuse of mediastinoscopy in this trial, and therefore the inclusion of patients not currently accepted to be suitable for surgery. Analysis was performed by intention to treat and therefore included the 37 patients who underwent exploratory thoracotomy only or no surgery in the analysis of the 71 patients in the surgical arm, undermining the conclusion that the result of radical radiotherapy was "somewhat better" than the result of "surgery."

The second influential randomized trial was published in 1994 in which patients who were diagnosed with SCLC on bronchoscopy, where the origin of the tumor could be identified preoperatively and who responded to initial chemotherapy were randomized to surgery or no additional treatment with an overall 2 year-survival of 20% in both arms and a study conclusion of no additional benefit of surgery.[5] In this study, 54/70 (77%) patients underwent complete resection and again the intention to treat analysis included 8 patients who refused surgery, 4 who had an incomplete resection, and 12 patients with unresectable disease. Although we do not contend that an intention to treat analysis was inappropriate, the failure to adhere to protocol renders the results of intention to treat analysis susceptible to bias. What is perhaps most difficult with trials that evaluate surgery as an adjuvant treatment modality is the conundrum that the surgeon faces at thoracotomy, to resect a clearance margin based on the operative findings, or a margin based on prechemotherapy defined disease. After all, the surgeon is not able to visualize the presence of microscopic residual disease that may be present after chemotherapy.

The pendulum of opinion may have swung too far against surgical treatment as an option in SCLC and it has become difficult for surgeons to justify the routine resection of limited stage small cell lung carcinoma patients based on the results of these two influential randomized trials. Some clinicians might even consider surgery inappropriate for patients who present with solitary pulmonary nodules that prove to be small cell lung cancer on fine needle aspiration biopsy.

Our surgical series suggests that good results can be achieved in selected patients with complete resection throughout the spectrum of UICC stage I to III. The results do not suggest that we should routinely operate upon all patients in stage I to III. However, the overall 5 year survival of 52% in our series does suggest the need for further randomized trials to clarify appropriate case selection for surgery in light of improved staging modalities (spiral CT, PET, magnetic resonance imaging, transthoracic needle aspiration biopsy, endoscopic esophageal ultrasound guided biopsy, and endoscopic transbronchial ultrasound guided biopsy). Perhaps the most influential of which has been PET with the ability to evaluate local, mediastinal and distant disease, certainly in the non-small cell setting.[11,12]

Clinical Staging

The currently accepted Veterans Administration staging criteria remains adequate when evaluating more extensive cases for chemotherapy and radiotherapy. Shepherd et al. [6] suggested a refinement to the Veterans Administration staging by introducing the "very limited" category in patients without evidence of mediastinal nodal disease. However, if surgery is to be considered as a treatment modality a more detailed clinical staging classification needs to be adopted, perhaps the most useful would be the TNM classification of lung cancer; it encompasses the subcategory of "limited" disease in the N2 designation and also allows the assessment of the extent of surgery required (T category). The N2 designation has traditionally been considered as a contraindication to surgery. While in this series, there were 3/7 and 6/16 patients on follow-up identified to have N2 disease on clinical and pathologic staging respectively these numbers are too small to offer definitive conclusions on patient selection. This underscores the heterogeneity of the spectrum of N2 designation ranging from bulky mediastinal node disease to occult metastasis identified only on histologic analysis of resected lymph nodes, and the need to avoid a blanket exclusion of the N2 subgroup from the possible beneficial effects of surgical resection.

Pathologic Staging

Clinical staging is often applied to guide management and pathologic staging to predict prognosis, although the two aims are often not mutually exclusive. In our series, the influence of nodal involvement was unclear; the best prognostic subgroup was in patients with N2 disease, as a result when the UICC stage grouping was applied, no clear discrimination in survival was obtained. This applied to both clinical and pathologic N categories. Adjuvant chemotherapy has been more rigorously evaluated in non-small cell cancer setting with meta-analysis of randomized trials reporting a 13% relative reduction in the hazard for death,[13] but less information is known in the small cell setting with some centers opting for routine adjuvant chemotherapy.[3]

Potential Limitations

We are aware of the limitations of our sample as only 26 deaths were experienced in our series, and the power of a survival analyses are derived from the number of events rather than the sample size. Our report may represent a chance finding of long term survival in our cohort. Another point of view is that the determinants of prognosis in completely resected small cell lung cancer are incompletely understood and patients with advanced stage (stage III) disease actually had long term survival. We accept that we have no information on open-and-close cases for SCLC during this time, nor did we have robust information on adjuvant treatment for inclusion in this study. Our institution is a tertiary referral center and many treated patients return to the care of their local oncologists, outside our catchment area.

CONCLUSIONS

With careful case selection, good results can be obtained for patients undergoing lung resection for limited disease small cell lung cancer when complete resection can be achieved. Randomized trials are required to assess the effects of surgery as part of multimodality treatment in the presence of improved staging modalities. More work is required to improve on existing clinical classification models for patients who are potentially suitable for surgery and to develop better prognostic models in patients who have undergone complete resection for small cell lung cancer.

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